PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Omega-3 polyunsaturated fatty acid supplementation for improving peripheral nerve health: protocol for a systematic review
AUTHORS	Zhang, Alexis; MacIsaac, Richard J.; Roberts, Leslie; Kamel, Jordan; Craig, Jennifer; Busija, Lucy; Downie, Laura

VERSION 1 – REVIEW

REVIEWER	Hércules Rezende Freitas Universidade Federal do Rio de Janeiro, Brazil.
REVIEW RETURNED	11-Dec-2017

GENERAL COMMENTS	The manuscript "Omega-3 polyunsaturated fatty acid supplementation for improving peripheral nerve health: protocol for a systematic review" is a well-written protocol article, providing all the elements necessary to ensure low bias in a quality systematic review. Essentially, authors structured their protocol according to the Cochrane Handbook for Systematic Reviews of Interventions, which is an establish guide for systematic reviews. I have, however, few concerns and recommendations to present before the manuscript is accepted for publication: - Authors shouldn't consider conference abstracts as eligible for inclusion in the study; or, at least, they should better explain the decision to include them; - Regarding the participant's age, as there's no age limit above 18 years old, and the elderly are a frequent public in trials with omega-3, authors should also provide a strategy to analyze the effects of omega-3 separately in two populations, younger adults and the elderly (e.g. > 60 y.o.). This, of course, if enough studies are included in the review; - In "Measuring of the treatment effect", authors state that "The effects of the interventions will be expressed as the mean difference (MD), with 95% confidence intervals (CIs), between the intervention and comparator groups". I believe that, if possible, authors should also use a 99% confidence interval measurement (p = 0.01) to separate between "significant" (p = 0.05) and "highly significant" (p = 0.01) differences between effect and null hypothesis distributions; - Finally, I'm not qualified to satisfactorily review the standard of written English throughout the manuscript, however, I haven't noticed major spelling errors while reviewing it. Nevertheless, I still recommend a full text review before acceptance.

	If the authors successfully address these comments, I have no further issues with publication of their manuscript in BMJ Open.

REVIEWER	Mark Yorek University of Iowa Iowa City, Iowa USA
REVIEW RETURNED	11-Dec-2017

GENERAL COMMENTS	This is a protocol report for a review article to analyze the efficacy of omega-3 polyunsaturated fatty acids on peripheral neuropathy. The protocol described is comprehensive. The authors will collect data from all reported available on the impact of omega-3 polyunsaturated fatty acids on peripheral neuropathy independent of cause. I question the amount of literature available on this topic. Other areas of concern there appeared to be no mention of the multiple differences and different study designs that will be encountered. It was also not mentioned if the authors when reviewing publication will consider whether the studies performed examined compliance related issues. A couple of other minor concerns: 1) On the bottom of paragraph 1 on page 5 the authors attempt to reference mechanisms that may be responsible for peripheral neuropathy. This list is incomplete and should be stated as such. 2) On the next paragraph the authors state that peripheral neuropathy correlated with the degree of glycemic control. This is only true for type 1 diabetes. It was not stated whether the authors will evaluate data from diabetic studies taking into consideration type 1 and type 2 diabetes. Peripheral neuropathy in the subjects with type 1 or type 2 diabetes is different.

VERSION 1 – AUTHOR RESPONSE

Reviewer's comments

Reviewer 1:

1. Authors shouldn't consider conference abstracts as eligible for inclusion in the study; or, at least, they should better explain the decision to include them.
The rationale for including published conference abstracts is to ensure that we maximise capture of the breadth of literature potentially relevant to the review topic, and thus minimise potential effects related to publication bias. It has been identified that more than half of clinical trials reported in conference abstracts never reach full publication (Scherer 2007). It is, therefore, important to try to identify possibly relevant studies reported in conference abstracts. Our approach to include conference abstracts is consistent with the inclusion criteria of rigorous systematic reviews, such as those performed by the Cochrane Collaboration. To avoid any potential duplication, we will only include in conference abstracts that do not report the same cohort of participants as full-text studies already included in the review.

2. Regarding the participant's age, as there's no age limit above 18 years old, and the elderly are a frequent public in trials with omega-3, authors should also provide a strategy to analyze the effects of omega-3 separately in two populations, younger adults and the elderly (e.g. > 60 y.o.). This, of course, if enough studies are included in the review.
We agree with the reviewer that age may affect intervention outcomes. To assess this potential effect, in our protocol, in the section titled 'subgroup analysis and investigation of heterogeneity' we have

specified that we intend to perform subgroup analyses by prognostic factors (e.g., age), if sufficient data are available.

3. In "Measuring of the treatment effect", authors state that "The effects of the interventions will be expressed as the mean difference (MD), with 95% confidence intervals (CIs), between the intervention and comparator groups". I believe that, if possible, authors should also use a 99% confidence interval measurement (p = 0.01) to separate between "significant" (p = 0.05) and "highly significant" (p = 0.01) differences between effect and null hypothesis distributions.
We thank the reviewer for this suggestion, and would like to highlight that for all analyses, we will report actual p-values, which will enable the readers to independently assess the level of evidence against the null hypothesis.

4. Finally, I'm not qualified to satisfactorily review the standard of written English throughout the manuscript, however, I haven't noticed major spelling errors while reviewing it. Nevertheless, I still recommend a full text review before acceptance.
We wish to reassure the reviewer that the English expression is of a suitable standard.

Reviewer 2:

1. I question the amount of literature available on this topic. Other areas of concern there appeared to be no mention of the multiple differences and different study designs that will be encountered.
We agree that the literature available on this topic may be narrow; the purpose of the systematic review is to identify, appraise and synthesise all relevant literature on this topic, to inform future research in the field.
This will be, to our knowledge, the first systematic review to consider the therapeutic effects of omega-3 supplementation on peripheral nerve integrity. In order to maximise the number of publications eligible for inclusion, we have not limited this review to a specific underlying condition, and will include all studies that examine the integrity of peripheral nerves in any location of the body.

We will conduct this systematic review using the approach recommended for intervention reviews in the Cochrane Handbook of Systematic Reviews, and thus we will include only randomised controlled trials. This approach minimises the potential confounding effects resulting from including studies that have adopted less robust designs. We will not include quasi-randomised controlled trials, as bias can be potentially introduced through unmeasured correlation between methods of group allocation and the outcome.

2. It was not mentioned if the authors when reviewing publication will consider whether the studies performed examined compliance related issues.
We thank the reviewer for this useful suggestion. We have incorporated this recommendation by adding a statement in the section on "Data extraction" that we will extract data relating to whether compliance measures were utilised and the method used (e.g., returned capsule counts, red blood cell fatty acid profiles) from each included study.

3. On the bottom of paragraph 1 on page 5 the authors attempt to reference mechanisms that may be responsible for peripheral neuropathy. This list is incomplete and should be stated as such.
We acknowledge that this sentence only includes some of the key potential mechanisms that can contribute towards the pathogenesis of peripheral neuropathy. To clarify this, we have amended this sentence to read: "Some of these mechanisms include altered metabolism and intracellular signaling,[3] vascular and inflammatory stress,[4] and reactive oxygen species formation[5]."

4. On the next paragraph the authors state that peripheral neuropathy correlated with the degree of glycemic control. This is only true for type 1 diabetes. It was not stated whether the authors will evaluate data from diabetic studies taking into consideration type 1 and type 2 diabetes. Peripheral neuropathy in the subjects with type 1 or type 2 diabetes is different.
The reviewer makes a valid point that the degree of glycaemic control is only currently highly correlated with peripheral neuropathy for type-1 diabetes; the most recent position statement by the American Diabetes Association (ADA) describes that enhanced glucose control is associated with a modest reduction in the relative risk of developing DSPN (5-9% relative risk) in people with type-2 diabetes (Pop-Busui 2017).

To address the reviewer's concerns that the effect of glycaemic control is potentially different with respect to risk of DSPN in type-1 and type-2 diabetes, we have amended the paragraph to state that the risk of neuropathy may be correlated with the degree of glycaemic control particularly in type-1 diabetes, replacing the term 'is', for its definitiveness. We have also additionally referenced the statement by the ADA and related studies.

With respect to whether we will evaluate data separately from studies that have evaluated participants with type-1 and type-2 diabetes, we have now included a provision to perform a sub-group analysis (in the section "subgroup analysis and assessment of heterogeneity") that considers the sub-type of diabetes as a prognostic factor.

VERSION 2 – REVIEW

REVIEWER	Mark Yorek University of Iowa United States
REVIEW RETURNED	22-Jan-2018

GENERAL COMMENTS	My concerns were addressed.

REVIEWER	Hércules Rezende Freitas Professor - GayLussac Institute Researcher - Federal University of Rio de Janeiro Rio de Janeiro, Brazil.
REVIEW RETURNED	22-Jan-2018

GENERAL COMMENTS	My major concerns were fully answered in the current version of the manuscript. Additional modifications are possibly of aesthetic nature and should be solved during proof preparation.